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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,089	02/11/2000	Amanda J. Patel	1201-CIP3-00	6089

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/503,089	PATEL ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,18-20,22,23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,18-20,22,23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 16, 2005 has been entered.

2. Claims 18, 22 and 23 have been amended. Claims 13-16, 18-20, 22, 23 and 25 are pending and under consideration.

3. Acknowledgement is made of the addition of F. Duprat and F. Maingret as inventor by the petition filed May 16, 2005. Acknowledgment is also made of the inclusion of M Fink as an inventor by the petition filed August 11, 2004.

4. Sections of Title 35, U.S. Code not found in the action can be found in a prior action.

5. Claims 18 and 22 are objected to because of the following informalities: The following typographical errors: clam 18, "molecure"; claim 22, "havign" and "tarnsfected".. Appropriate correction is required.

6. Review and reconsideration of a claim to an earlier effective filing date via 09/144,914, filed September 1, 1998, 08/749,816, filed November 15, 1996 and 60/095,234, filed August 4, 1998 has been made. However, it is concluded that none of the prior applications disclose SEQ ID NO:2, the '816 application discloses only a partial sequence of SEQ ID NO:4, and none of the applications provide a written description of the instant methods of screening for substances having anesthetic properties which produce a reversible state of unconsciousness with amnesia and analgesia in a mammal upon inhalation. The priority date for all the instant claims is effective filing date of February 11, 2000.

7. Claims 14-16, 18, 22 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) It is unclear how claims 14 and 15 further limit claim 13, because it is unclear if the recitation of TASK and TREK is limited to SEQ ID NOL2, 4 or 5, or if said recitation encompasses variants of SEQ ID NO:2, 4 and 5 that are at least 95% identical to SEQ ID NO; 2, 4 and 5.

(B) Claim 18, the recitation of "TREK-1" in part (b) lacks antecedent basis in part (a).

(C) Claim 18 recites "said potassium channel is selectively activated by chloroform, diethyl ether, halothane and isoflurane". Claim 22 recites "said TASK is selectively activated by halothane and isoflurane". It is unclear if these chemicals are being referred to collectively or in the alternative. Amendment of the claims to recite "or isoflurane" rather than "and isoflurane" will overcome this part of the rejection.

(D) Claim 22 recites "an amino acid sequence according to SEQ ID NO:5". The metes and bounds of "according to" cannot be determined, and it is unclear if the claim encompasses sequences comprising or consisting of SEQ ID NO:5 or fragments of SEQ ID NO:5.

8. The rejection of claims 13-16, 18-20 under 35 U.S.C. 102(a) as being anticipated by Patel et al (Nature Neuroscience, 1999, Vol. 2, pp. 422-426) is maintained for reasons of record. Claims 22, 23 and 25 are also rejected for the same reasons of record since priority to an earlier effective filing date is not recognized for the instant claims.

Claim 13 is drawn to a method for identifying substances having anesthetic properties, wherein said substances produce a reversible state of consciousness with amnesia and analgesia in a mammal upon inhalation, said method comprising contacting said substances with TREK-1 or TASK or variants of TREK-1 or TASK having at least 95% sequence identity to SEQ ID NO:2 , 4 or 5, wherein SEQ ID NO:2, 4 or 5 are mammalian transport proteins which exhibit outward-going potassium rectification, and determining the potassium transport of said TREK-1 or TASK protein wherein an activation of potassium transport activity is indicative that said substance has anesthetic properties. Claims 14 and 15 embody the method of claim 13 wherein said potassium transport proteins is TASK or TREK-1 , respectively. Claim 16 embodies the

method of claim 15 wherein said TREK-1 comprises either SEQ ID NO:2 or SEQ ID NO:4. Claim 18 is drawn to a method for identifying substances having anesthetic properties wherein said substance produce a reversible state of consciousness with concurrent amnesia and analgesia upon inhalation be a mammal comprising contacting said substance with COS cells wherein said COS cells are transfected with a nucleotide vector comprising a nucleic acid molecule encoding a potassium channel comprising SEQ ID NO:2, SEQ ID NO:4, amino acid sequence having at least 90% identity to SEQ ID NO:2 and amino acid sequence having at least 90% identity to SEQ ID NO:4, wherein said COS cells transiently express said potassium channel, wherein said potassium channel exhibits outward going potassium rectification; and wherein said potassium channel is selectively activated by chloroform, diethyl ether, halothane and isoflurane, and determining the potassium transport activity of said TREK-1 wherein an activation of potassium transport is indicative of said substance having anesthetic properties. Claim 19 is drawn to a method for identifying substances having anesthetic properties wherein said substance produce a reversible state of consciousness with concurrent amnesia and analgesia upon inhalation be a mammal comprising contacting said substance with COS cells wherein said COS cells are transfected with a nucleotide vector comprising SEQ ID NO:2, wherein said COS cells transiently express the protein encoded by SEQ ID NO:2 and wherein said protein exhibits outward going potassium rectification; and determining the potassium transport activity of said protein wherein an activation of potassium transport is indicative of said substance having anesthetic properties. Claim 20 is drawn to a method of identifying substances having anesthetic properties wherein said substance produce a reversible state of consciousness with concurrent amnesia and analgesia upon inhalation be a mammal comprising contacting said substance with COS cells wherein said COS cells are transfected with a nucleotide vector comprising SEQ ID NO:4, wherein said COS cells transiently express the protein encoded by SEQ ID NO:4 and wherein said protein exhibits outward going potassium rectification; and determining the potassium transport activity of said protein wherein an activation of potassium transport is indicative of said substance having anesthetic properties. Claim 22 is drawn to a method for identifying a substance having anesthetic properties wherein said substance produces a reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising contacting said substance with transfected cells, wherein said cell are transfected

with a nucleotide vector encoding TASK having an amino acid sequence according to SEQ ID NO:5 or an amino acid sequence that is at least 90% identical to SEQ ID NO:5 wherein said transfected cells transiently express said TASK, and wherein said TASK exhibits outward going potassium rectification and wherein said TAKS is selectively activated by halothane and isoflurane and determining the potassium transport activity of said TASK, wherein an activation of potassium transport us indicative of said substance having anesthetic properties. Claim 23 is drawn to a method for identifying a substance having anesthetic properties wherein said substance produces a reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising contacting said substance with transfected cells, wherein said cell are transfected with a nucleotide vector encoding SEQ ID NO:5 wherein said transfected cells transiently express said TASK, and wherein said TASK exhibits outward going potassium rectification and wherein said TAKS is selectively activated by halothane and isoflurane and determining the potassium transport activity of said TASK, wherein an activation of potassium transport us indicative of said substance having anesthetic properties. Claim 23 embodies the method of claim 22 wherein the transfected cells are selected from the group consisting of COS cells, HeLa cells, Spodoptera cells, Xenopus oocytes, embryonic kidney cells, CHO cells and fibroblasts.

Patel et al disclose a method for identifying substances having anorthic properties upon inhalation comprising contacting said substance with TREK-1 (mouse and human) or TASK expressed on the surface of COS cells (pages 422-425, under "Results"). It is noted that human TREK-1 is SEQ ID NO:2 and mouse TREK-1 is SEQ ID NO:4 and that activation of potassium transport in the TREK-1 or TASK proteins was observed by outward-going potassium rectification (page 423, second column, lines 3-6).

9. Applicant argues that the inventive entities of Patel et al (Nature Neuroscience, 1999) and the instant claims are the same. However, this is found not to be correct.

PATEL(1999)	INSTANT
Patel	Patel
Honore	Honore

Lesage	Lesage
Fink	Fink
Romey	Romey
Lazdunski	Lazdunski
	Duprat
	Maingret

Clearly, the inventive entity differs between Patel (1999) and the instant invention. Applicants arguments are therefore moot.

10. The rejection of claims 13-16, 18 and 20 under 35 U.S.C. 103(a) as being unpatentable over Franks and Lieb (Nature, 1988, vol. 333, pp. 662-664, cited in a previous Office action) in view of Patel et al (EMBO, 1998, Vol. 17, pp. 4283-4289, reference AN of the IDS filed February 11, 2000) are maintained for reasons of record. The specific embodiments of the claims are recited above.

Franks and Lieb teach a direct correlation between the presence of an anesthetic-induced current, Ik(an) and anesthetic-induced inhibition of spontaneous firing in a given neurons and that those neurons which were insensitive to anesthesia lacked the Ik(an) current while said current was always present in a sensitive cell. Franks and Leib teach that such anesthesia activated potassium channels have just the properties that might be expected for the principle target sites involved in general anesthesia (page 664, first column, lines 34-36).

Patel et al (1998) teach that TREK-1 encodes a mammalian mechano-activated potassium channel which shares most of the properties of the Aplysia S-type potassium channel (page 4283, second column, last 4 lines). Patel et al compare the opening of the TREK-1 potassium channel by chloroform with the opening of the Aplysia channel by chloroform (page 4286, bridging paragraph and legend for Figure 1). Patel et al especially note that the I-V curve of the chloroform activated current in TREK-1 is identical to the AA-sensitive current. Further both the Aplysia S channel and the TREK-1 channel are both mechano-activated (page 4285, second column, lines 16-21). It is noted that Patel et al teach mouse TREK-1 which is SEQ ID NO:4

It would have been prima facie obvious to one of skill in the art at the time the invention was filed to substitute the measurement of the Ik(an) current in TREK-1 for the measurement of the Ik(an) current of the Aplysia-S channel. One of skill in the art would be motivated to do so by the teachings of Patel et al on the similarities between the current induced by anesthesia in the TREK-1 potassium channel and the current induced by the Aplysia S channel in response to general anesthetics. One of skill in the art would be motivated to identify substances having the property of inducing said Ik(an) current by the teachings of Franks and Lieb on the targeting of said current by general anesthesias and additionally because the mammalian homologue of the Aplysia S-channel would be more appropriate in the screening of said substances, as one of skill in the art would recognize that said substance would the have the potential of being used clinically to induce reversible unconsciousness in a mammalian subject.

11. Applicant argues that Patel (1998) was not published one year prior to the priority date for the instant invention. Applicant argues that the provision application describes methods for identifying substances capable of producing amnesia and analgesia but does not provide page and line numbers from the provisional application to support this allegation. The provisional application, and the '814 and '916 applications have been reviewed and found not to mention the reversible induction of unconsciousness, a sleep like state, or somnolence upon exposure of the instant TASK or TREK proteins to volatile anesthetics and thus does not provide an adequate written description of the instant method claims. Further, as stated above, none of the prior applications disclose SEQ ID NO:2, and the '816 application discloses only a partial sequence of SEQ ID NO:4. Thus, applicants arguments regarding the effective filing date are moot.

12. Claims 13-15, 18, 19, 20, 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying substances having anesthetic properties, wherein the TREK, and TASK proteins comprise SEQ ID NO:2, 4 or 5, does not reasonably provide enablement for a method of identifying substances having anesthetic properties, wherein the TREK, and TASK proteins are at least 95% identical to SEQ ID NO:1, 3 or 5, TREK proteins are 90% identical to SEQ ID NO:2 ,4 or 5, or nucleic acid molecules encode "an" amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:4, or "an" amino acid

sequence according to SEQ ID NO:5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not teach how to make said variants which differ from the amino acid sequences of SEQ ID NO:2, 4 or 5, but which function as claimed. Further, claims 18, 19, 20, 22 are specifically drawn to "an amino acid sequence" of SEQ ID NO:2, 4, or 5 and an amino acid sequence of 90% variants of SEQ ID NO:2, 4 and 5, which when given the broadest reasonable interpretation read on a fragment of SEQ ID NO:2, 4 and 5 and fragments of 90% variants of SEQ ID NO:2, 4 and 5. The specification does not teach a fragment of SEQ ID NO:2, 4 or 5 which would retain the functional activity of SEQ ID NO:2, 4 or 5 with respect to activation by inhalation of isoflurane or halothane.

Bowie et al (Science, 1990, Vol. 257, pp.1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to

ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (Journal of Cell Biology, 1990, Vol. 11, pp. 2129-2138, cited in a previous Office action) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the growth factor and by Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252, cited in a previous Office action) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the altered TGF-alpha. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Leonoudakis et al (Journal of Neuroscience, 1998, Vol. 18, pp. 868-877) teach that rat TASK (rTASK) which is 90.6% identical to the instant SEQ ID NO:5 did not respond to isoflurane (page 872, second column, lines 23-26). This reference further supports the unreliability in the art of determining the function of a protein based on sequence homology because rat TASK which has the required degree of homology with an amino acid sequence having 90% identity to SEQ ID NO:5 does not function as claimed. Given the lack of teachings in the specification which address the unreliability in the art as stated above, one of skill in the art would be subject to undue experimentation in order to make the protein variants and fragments on which the instant method claims depend.

13. All other rejections and objections as set forth in the previous Office action are withdrawn.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/25/2005

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER